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Abstract

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Project Title:	High Throughput Screening for Protein Misfolding Disease Therapeutics

Abstract: *DESCRIPTION (provided by applicant):* The most important objective of the proposed screen is to identify folding modulators, small molecules that enable misfolding prone proteins to be folded in the cell and to be trafficked to their destination, avoiding loss-of-function misfolding diseases. Numerous genetic diseases are caused by misfolding, or the failure of a mutated protein to assume its native active conformation. The distinct advantage of molecules that enhance the folding capacity of the endoplasmic reticulum and/or cytoplasm within the cell is that one or a few molecules could be used to treat multiple loss-of-function diseases. Such an approach is significant because although many of these diseases affect a small number of patients, in aggregate, there are, hundreds of thousands of people suffering of loss-of-function misfolding disease. We employ Gaucher disease, a disorder due to loss-of-function of the enzyme b-glucocerebrosidase (GC), as a representative loss-of-function misfolding disease, and employ patient-derived cells for the discovery of small molecule folding modulators - molecules that enhance the ability of the endoplasmic reticulum to fold, and enable trafficking of GC to the lysosome. Specifically, we utilize the L444P GC patient-derived cell line, which affords active GC when grown at 30 xC, but not when grown at 37 xC, even in the presence of chemical chaperones (molecules that bind to GC active site, and stabilize several variant GC in the ER, enabling them to be trafficked to the lysosome). We employ L444P GC fibroblasts for a high throughput cell-based screen to seek compounds that restore the compromised cellular GC activity at 37 xC associated with Gaucher disease. Putative folding modulator hits will be confirmed by their ability to fold and traffic the mutant chloride channel whose absence is associated with the development of cystic fibrosis. In parallel, a second high throughput screen will be performed using a Gaucher disease cell line amenable to GC specific chemical chaperoning. The N370S GC cell line will be used to select pharmacologically appealing compounds for ameliorating Gaucher disease affecting the central nervous system, which represents a currently unmet medical need.

Thesaurus Terms: folding modulators, small molecules, endoplasmic reticulum, loss-of-function misfolding disease, Gaucher disease, b-glucocerebrosidase, GC, chemical chaperones, L444P GC fibroblasts, high-throughput screening, HTS, cell-based screen, N370S GC, central nervous system, CNS

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